## Remarks

Reconsideration of this application is respectfully requested.

### A. Objection to the Drawings

The objection to the drawings is noted. Applicants will submit formal drawings upon allowance of the application.

### B. In the Specification

Substitute Figures 14, 18, 19, 26, 27, and 28 have been amended merely to include the appropriate SEQ ID NO for the nucleotide or amino acid sequence depicted in the figure. Also, as the sequence in Figure 14 spans multiple pages, substitute Figure 14 has been amended to label each page as 14A-14J.

The specification has also been amended to reinsert the sequence identifiers, SEQ ID NO: 10, SEQ ID NO: 22, and SEQ ID NO: 23, as requested by the Office.

In addition, the specification has been amended to provide antecedent basis for the claimed subject matter, as requested in the Office Action (paragraph 8). As stated by the Examiner, support for the amendment is found in original claim 4. Accordingly, no new matter has been added by way of the amendment.

### C. In the Claims

Claims 1-6 have been amended to recite that the multiple toxicity-associated regions are localized to amino acids 231-238 and 310-331 of the $CH_2$ domain. Support for the amendment can be found throughout the specification and particularly at, for example, pages 10, lines 8-15 and pages 21-23 and 25-26.

Claims 1-6 have also been amended merely to provide proper antecedence to the claims.

New claims 53-64 have been added. Support for the new claims can be found throughout the specification and in the original claims.

No new matter has been added by way of the amendments.

## D. Associate Power of attorney

Applicant submits herewith an associate Power of Attorney for Emily Miao, Anita J. Terpstra, and Paul H. Berghoff of the law firm of McDonnell Boehnen Hulbert & Berghoff (Customer no. 020306) from an attorney or agent of record. Accordingly, Anita J. Terpstra is now an attorney of record via the associate Power of Attorney document.

## E. The 35 USC § 112, Second Paragraph, Rejections

Claims 1-6 have been rejected under 35 USC § 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse the rejection.

The Office contends that the claims are indefinite because one would not be able to localize amino acids 231-238 and 310-331 in generic immunoglobulins without knowing how to number the amino acids in the $CH_2$ domain and where exactly the numbering of amino acids starts within a specific sequence. Applicants submit that the claims are clear and definite because one skilled in the art of immunology would know how to number the amino acids in the $CH_2$ domain and thus would be able to locate the appropriate amino acids in a generic immunoglobulin. Moreover, the specification teaches that the system of amino acid position numbering is found in Kabat et al., Sequences of Proteins of Immunological Interest, 5$^{th}$ Ed. (1991). (Specification at page 21, lines 27-29).

Claims 1-6 have also been rejected under 35 USC § 112, second paragraph, because the Office maintains that it is not clear whether the second recitation of "a subject" is intended to mean the same subject as that of the first recitation or is intended to mean a different subject. Claims 1-6 have been amended to recite "said subject" in the second recitation, thereby obviating the rejection by providing proper antecedence.

For the reasons set forth above, Applicants submit that the claims are clear and definite. Accordingly, Applicants respectfully requests withdrawal of the 35 USC § 112, second paragraph, rejections.

## F. The 35 USC § 112, First Paragraph, Rejections

### *1. New Matter*

Claims 1-6, 8-22, and 28-31 have been rejected under 35 USC § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Specifically, the Office contends that there is no descriptive support in the instant application as originally filed to support the new limitation: wherein multiple toxicity-associated regions consist of amino acids 231-238 and amino acids 310-331.

While Applicants do not acquiesce with the Office's rejection, solely in an effort to advance prosecution, claims 1-6, 8-22, and 28-31 have been amended to recite: wherein multiple toxicity-associated regions are localized to amino acids 231-238 and amino acids 310-331, thereby obviating the rejection. Accordingly, Applicants respectfully request withdrawal of the new matter rejection with respect to these claims.

***2. Enablement***

Claims 1-6, 8-12, 15, 16, 19, 20, and 28-31 have been rejected under 35 USC § 112, first paragraph, as allegedly not enabling one skilled in the art to make and/or use the invention commensurate in scope with the claims. Specifically, the Office contends that the specification does not reasonably provide enablement for a method of inhibiting immunoglobulin-induced toxicity in any human or non-human subject comprising administering an immunoglobulin of any class or subclass, which is structurally altered at multiple toxicity-associated regions that consist of amino acids 231-238 and 310-331 of the $CH_2$ domain of the immunoglobulin. Applicants respectfully traverse the rejection.

The test of enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the patent coupled with information known in the art (3) without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); M.P.E.P. § 2164.01.

The instant specification thoroughly teaches a method for inhibiting immunoglobulin-induced toxicity using an immunoglobulin that has been structurally altered in multiple toxicity-associated regions localized to amino acids 231-238 and amino acids 310-331 of the $CH_2$ domain. First, the specification teaches one skilled in the art how to make the recited immunoglobulin. For example, the specification teaches the position of the amino acids associated with immunoglobulin toxicity in the $CH_2$ region (pages 10) and provides numerous examples of structural alterations that can be made (pages 4, 10-11, 14-15), including which specific mutations can be made (pages 21-26). The

specification further teaches different methods for structurally altering (mutating) immunoglobulins in multiple toxicity-associated regions (pages 28-34, 38-47 and Figures). The specification also teaches methods for using the structurally altered immunoglobulins to inhibit immunoglobulin-induced toxicity (pages 12, 16-17, and 19-21). In addition, the specification teaches one how to test immunoglobulin or antibody activity (pages 29-30 and 48-49 and Figures 1, 7, 8, 15, 22, and 23), as well as test for inhibition of immunoglobulin-induced toxicity (pages 15 and 34-37). Finally, the specification provides *in vitro* data (page s 48-49, Figures 20 and 21) and *in vivo* data (pages 34-37) to demonstrate that immunoglobulins structurally altered in multiple toxicity-associated regions localized to amino acids 231-238 and 310-331 work to alleviate immunoglobulin-induced toxicity. Specifically, the *in vitro* data shows that several immunoglobulins having various structural alterations in amino acids 231-238 and 310-331 of the $CH_2$ domain exhibit less complement dependent activity and less antibody dependent cell-mediated cytotoxicity than control immunoglobulins. The *in vivo* data shows that an immunoglobulin having its entire CH2 region deleted (cBR96-A) inhibits immunoglobulin-induced gastrointestinal toxicity in canines. Other experiments show that an immunoglobulin having mutated amino acids at positions 235 and 237 in the CH2 domain (hBR96-2B) inhibits immunoglobulin-induced gastrointestinal toxicity in canines (page 37 and 44-46).

While the Office acknowledges that the specification describes several different IgG immunoglobulins having mutations in amino acids 231-238 and 310-331 of the $CH_2$ domain, the Office argues that the claims are not enabled because one would not be able to identify the multiple toxicity-associated regions localized to amino acid positions 231-238 and 310-331 in other classes of immunoglobulins because the instant specification does not provide adequate guidance as to where to start the amino acid numbering within the $CH_2$ region for each immunological class, subclass, or isotype. Thus, the Office concludes that the recited amino acid positions are relevant to the exemplified BR96 antibody only and not to a generic immunoglobulin in a different class, sub-class or isotype.

However, as discussed previously, one skilled in the art of immunology would know how to number the amino acids in the $CH_2$ domain. Further, the specification teaches the amino acid numbering system used. Thus, one skilled in the art would be able to apply the amino acid numbering system described in the specification to determine the location of amino acids 231-238 and 310-331 in a generic immunoglobulin.

Furthermore, despite the considerable teachings in the specification, the Office contends that the claims are not enabled for a method of inhibiting immunoglobulin-induced toxicity using an immunoglobulin of any class, subclass, or isotype having the recited structural alterations in the recited areas of the $CH_2$ domain because the specification only provides *in vivo* data for one structurally altered immunoglobulin which is deleted of the $CH_2$ domain. The Office concludes that in the absence of *in vivo* data or correlative *in vitro* data, the inhibition of immunoglobulin-induced toxicity can not be predictably produced by the recited structural alterations in a generic immunoglobulin of any class, subclass, or isotype.

First, while the Office states that there "is no evidence of record showing that any other immunoglobulin other than CH2-deleted BR96 is indeed administered to a subject", Applicant points out that the hBR96-2B, an immunoglobulin having mutated amino acids at positions 235 and 237 in the $CH_2$ domain, was administered *in vivo* and shown to inhibit immunoglobulin-induced toxicity (page 37).

In addition, contrary to the Office's allegation, the specification provides correlative *in vitro* data for several immunoglobulins having the recited structural alterations in the recited areas of the $CH_2$ domain. The specification teaches that the constant region can promote cell death through antibody dependent cell mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC) (page 2). The specification further teaches that amino acids in multiple toxicity associated domains in the constant region can be altered so as to render the constant region unable to mediate a ADCC response or activate complement (CDC response), thereby inhibiting immunoglobulin induced toxicity (page 4, 10-11, and 15). Thus, determining the level of ADCC or CDC response is a method for measuring the level of immunoglobulin induced toxicity. The specification further teaches that *in vitro* assays for determining whether the immunoglobulin is able to inhibit ADCC or CDC response is well-known in the art and provides several references teaching such methods (page 15).

The specification provides several different immunoglobulins with the following mutated amino acids: (1) hBR96-2B (235, 237); (2) hBR96-2C (318, 320, 322); (3) hBR96-2D (331); hBR96-2E (235, 237, 318, 320, 322); (4) hBR96-2F (235, 237, 331); (5) hBR96-2G (318, 320, 322, 331); hBR96-H (235, 237, 318, 320, 322, 331); and hBR92-2A (entire CH2 domain deleted). Of these, hBR96-2B, -2C, -2D, -2H, and -2A were tested *in vitro* for ADCC and CDC response and shown to exhibit decreased immunoglobulin induced toxicity.

Further, as discussed above, the specification teaches one skilled in the art how to make an immunoglobulin structurally altered in multiple toxicity-associated regions localized to amino acids 231-238 and amino acids 310-331 of the $CH_2$ domain and also teaches one how to test for inhibition of immunoglobulin-induced toxicity using *in vitro* and *in vivo* methods. Employing the methods taught in the specification, one skilled in the art would have been able to make and test additional immunoglobulins in other classes or subclasses having the recited structural alterations as a matter of routine experimentation.

In this regard, the law clearly states that "a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands,* 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Further, the fact that experimentation may be complex does not necessarily make it undue. *Massachusetts Institute of Technology v. A.B. Fortia,* 774 F.2d 1104 (Fed. Cir. 1985); *In re Wands,* 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Thus, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, is it undue. *In re Angstadt,* 537 F.2d 498 (CCPA 1976). Applicants submit that the methods used to make and test additional immunoglobulins (such as sequencing, mutagenesis, and screening for inhibition of toxicity), performed in accordance with the teachings of the specification, would involve well-established techniques that one skilled in the art would perform as a matter of routine experimentation.

The Office finally argues that the claims are not enabled for a method of inhibiting immunoglobulin-induced toxicity using a structurally altered immunoglobulin in any subject, human or nonhuman, because the specification only shows *in vivo* data for the administration of a structurally altered immunoglobulin to canines.

However, as stated in the specification, the *in vivo* canine model is a predictive model for *in vivo* activity in humans. (Specification at pages 36-37). As established by the Federal Circuit, "if the art is such that a particular model is recognized as correlating to a specific condition then it should be accepted as correlating *unless the Examiner has evidence that the model does not correlate.*" MPEP 2164.02 [emphasis added]; *In re Brana,* 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). Further, "[a] rigorous or an invariable exact correlation is not required." M.P.E.P. § 2164.02; *see Cross v. Iizuka,* 224 USPQ 739, 747 (Fed. Cir. 1985). Thus, one of ordinary skill in the art would recognize that the results of the *in vivo* canine model demonstrated in the instant application would be reasonably predictive of *in vivo* activity in humans.

For the reasons set forth above, Applicants submit that the claims are enabled. Accordingly, Applicants respectfully request withdrawal of this 35 USC § 112, first paragraph, rejection.

## G. Conclusion

In view of the remarks above, the application is considered to be in good and proper form for allowance and the Patent Office is respectfully requested to pass the application to issue. If, in the opinion of the Patent Office, a telephone conference would expedite the prosecution of this application, the Office is invited to call the undersigned attorney.

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Respectfully submitted,

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